

Therapeutic Review

Treatment of methanol poisoning with ethanol and hemodialysis

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Twelve cases of methanol poisoning are reviewed. The clinical presentation and biochemical features are described and the results of treatment with alkali, ethanol and dialysis reported. The outcome of methanol poisoning appears to be related more to the interval between the time of ingestion and the start of therapy and to the degree of acidosis than to the initial serum methanol level. Therefore, early and aggressive treatment with bicarbonate and ethanol and subsequent institution of hemodialysis are strongly recommended whenever methanol can be detected in the blood, especially when metabolic acidosis of the anion-gap type is present, when mental or visual disturbances are present, or when more than 30 ml of absolute methanol has been consumed.

Douze cas d'empoisonnement au méthanol font l'objet de cet article. On en décrit le tableau clinique et les caractéristiques biochimiques, et on rapporte les résultats de traitement obtenus avec les bases, l'éthanol et la dialyse. Les conséquences d'un empoisonnement au méthanol semblent davantage reliées à l'intervalle écoulé entre l'ingestion et le début du traitement et au degré d'acidose qu'à la concentration initiale de méthanol dans le sérum. En conséquence, un traitement immédiat et agressif avec du bicarbonate et de l'éthanol et l'institution subséquente d'une hémodialyse sont fortement recommandés chaque fois que du méthanol est décelé dans le sang, surtout quand il y a une acidose métabolique de type trou anionique, en présence de troubles mentaux ou visuels, ou quand plus de 30 ml de méthanol absolu ont été consommés.

The treatment of methanol poisoning has long interested toxicologists. An overdose is almost always due to ingestion of methanol as a substitute for ethanol. The symptoms of methanol poisoning, which may not appear for 12 to 24 hours, include visual disturbances, nausea, abdominal and muscle pain, dizziness, weakness and disturbance of consciousness ranging from coma to clonic seizures. Although a specific diagnosis depends on the demonstration of methanol in the blood, the principal clinical feature is severe metabolic acidosis of the anion-gap type.

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Even after a substantial delay, the level of intoxication may be effectively reduced by retarding the metabolism of methanol with the use of ethanol. In addition, hemodialysis is a useful form of therapy because methanol and its metabolites are easily dialysed.

We describe our experience with 12 patients with methanol poisoning and propose a standard form of management for such patients.

Patients and methods

We studied 12 patients with methanol poisoning: 4 had been seen by us and 8 had been identified by a search of medical records at the Toronto General Hospital for all patients who had been discharged with a diagnosis of methanol poisoning between 1975 and 1981 inclusive.

The serum methanol and ethanol levels were determined by gas-liquid chromatography at the Addiction Research Foundation of Ontario. The initial blood-gas and electrolyte determinations were performed in various laboratories (since many hospitals had referred the patients) by standard automated pH and blood-gas analysis, flame photometry and chloride titration.

Hemodialysis was performed with either a Drake Willock single-pass delivery system (DWS Inc., Portland, Oregon) or a CDAK (Cordis Dow artificial kidney) model 5 hollow-fibre dialyser (Cordis Dow Corp., Miami, Florida). A dialyser coil with a surface area of 2.5 m² was used. The rates of blood flow were determined by measuring the bubble transit time over a predetermined distance, and dialysance was calculated with the formula $D = Q(A-V)/A-B$, where D is the dialysance, Q is the rate of blood flow in millilitres per minute, A is the methanol concentration on the arterial side of the dialyser and V the concentration on the venous side of the dialyser, both in milligrams per decilitre, and B is the concentration of methanol in the dialysate, as has been suggested for a single-pass dialysate system.¹

To maintain a serum ethanol level greater than 100 mg/dl, ethanol was given in an oral loading dose of 0.6 to 1.0 g/kg body weight either as absolute ethanol or as a 50% solution. This dose was followed by a maintenance dose of 10 to 15 g of ethanol per hour given either as a 20% to 50% solution by mouth or as a 5% to 10% solution intravenously. The same ethanol concentration was maintained in the dialysate for the patients who

underwent hemodialysis. Serial serum ethanol levels were determined in all cases, and the treatment with ethanol was adjusted accordingly.

All 12 patients were treated with ethanol drips and sodium bicarbonate administered intravenously; 9 underwent hemodialysis and 1 peritoneal dialysis. Vascular access for hemodialysis was obtained by either placement of a prosthetic (Scribner) arteriovenous shunt (in two patients) or percutaneous venous cannulation (in seven patients). An acetate bath was used for dialysis in six of the nine patients, and a bicarbonate bath was used in the other three. Hemodialysis was carried out for 3 to 17 hours; it was continued until methanol could no longer be detected in the blood or until the patient died.

Results

The clinical presentation and biochemical findings in the 12 cases are summarized in Table I. The methanol levels and arterial blood-gas and electrolyte determinations were obtained from the blood sample taken at the time of the patient's admission to hospital.

Eleven of the patients had been transferred from other hospitals; except for one patient the diagnosis of methanol poisoning had been made at the time of admission to the referring hospital. Treatment with alkali and ethanol had been started before the transfer in all but two patients: in one the diagnosis had not yet been made and in the other the diagnosis had been made but treatment had not been started. Four of the patients had ingested the methanol accidentally and four had used it in an attempt to commit suicide; the circumstances were unknown for the other four patients. Nine of the patients had consumed methanol only and three had consumed it in combination with other intoxicants (ethanol in two and acetylsalicylic acid in one). The amount of methanol consumed varied from approximately 114 g of 20% methanol to 710 g of a methyl hydrate solution presumed to be 20% methanol. The amount was not known for five patients.

Most of the patients had been admitted to hospital with coma or a markedly decreased level of consciousness; one patient (no. 11) was alert despite a serum methanol level of 2649 mg/l. Abdominal pain was

present in three patients, one of whom demonstrated the clinical picture of pancreatitis — marked epigastric pain, nausea, vomiting and a serum amylase level of 740 (normal value 75 to 150) Somogyi units/l. Five of the patients had hemodynamic problems, hypotension being present at the time of admission or developing shortly thereafter. Two of the patients were blind.

In the four patients for whom there were sufficient data for the calculation, the dialysance of methanol varied from 100 to 200 ml/min and was dependent on the rate of blood flow.

Of the 12 patients 6 survived, although 1 remained legally blind, with dense central scotomata and marked impairment in visual acuity. Of the nine patients who underwent hemodialysis, five survived, including the blind patient. One patient, who was blind at the time of admission, improved rapidly with hemodialysis, such that his visual acuity returned to normal. The one patient treated with peritoneal dialysis died.

There were no complications of dialysis other than in patient 4, in whom pulmonary and gastrointestinal hemorrhage associated with systemic heparinization during dialysis occurred following 16 hours of hemodialysis and progressive hypotension. Only one patient (no. 2) required constant vasopressor support during dialysis.

The outcome in each of our patients can be related to the initial serum methanol level, the degree of acidosis, the interval between ingestion of the methanol and the start of treatment, and the serum bicarbonate level. The initial serum methanol level did not vary significantly between the patients who survived and those who died. However, there was a significant difference in the degree of metabolic acidosis, as shown by the presence of acidemia, an increased anion gap and a decreased serum bicarbonate level among those who died (group *t*-test). The serum bicarbonate level was particularly discriminating: in the six patients who died the level was less than 10 mmol/l, while in five of the six patients who survived it was more than 12 mmol/l. The interval between ingestion of the methanol and the start of therapy was also significant: four of the surviving patients were treated within 8 hours, whereas all the patients who died were without treatment for at least 24 hours.

Table I—Clinical presentation and biochemical findings at the time of admission of 12 patients with methanol poisoning

Patient no.	Sex/age (yr)	Interval between ingestion and start of therapy (h)*	Clinical presentation	Serum methanol level (mg/l)†	pH	Anion gap/serum bicarbonate level (mmol/l)	Outcome
1	M/44	Unknown	Coma	650	6.67	40/7	Died
2‡	M/52	Unknown	Coma	1011	6.80	51/5	Died
3	M/30	Unknown	Coma	2700	6.70	65/9	Died
4	M/87	Unknown	Coma	640	7.20	37/6	Died
5	F/63	Unknown	Agitated	827	6.80	37/6	Died
6	M/36	Unknown	Coma	4200	6.78	38/5	Died
7‡	M/42	< 4	Drowsy	4200	7.09	44/14	Alive
8	F/31	Unknown	Hysteria, abdominal pain	1050	6.81	50/15	Alive; blind
9	F/47	Unknown	Coma	4642	7.26	24/15	Alive
10‡	M/37	~ 8	Drowsy	420	7.42	21/15	Alive
11‡	M/61	< 4	Alert	2649	7.24	29/13	Alive
12‡	M/42	< 4	Coma, blind	4100	6.90	50/5	Alive

*Although the histories were vague in the cases with an unknown interval the mode of presentation and the best estimates after a review of the charts suggested an interval of at least 24 hours.

†Precision of measurement \pm 10%.

‡Chronic alcoholics.

Typical serial methanol and ethanol levels in the blood are given for two of the patients who underwent hemodialysis in Table II. The serum methanol levels decreased steadily during treatment, while the serum ethanol levels increased progressively during hemodialysis, although they varied considerably despite the similar treatment regimens.

In one patient (no. 2) a detailed postmortem examination revealed marked cerebral edema, extensive infarction of the putamen and internal capsule bilaterally, and extensive demyelination of the optic nerves.

Discussion

Metabolism and toxicity of methanol

The metabolism of methanol has been studied extensively in both animals and humans since the large-scale epidemics of methanol poisoning in the early 1930s and the prohibition era.^{2,3} Although some of the methanol is eliminated by the lungs in expired air,⁴ the main route of metabolism in humans appears to be through successive oxidation by alcohol dehydrogenase to formaldehyde and then formic acid. The oxidation usually occurs in the liver, but some occurs in the kidney and probably the gastrointestinal tract, areas where the highest concentrations of methanol are found. The half-life of methanol in humans is not known, although studies in animals have suggested that it is 24 to 60 hours.⁵ To what extent the rate of methanol metabolism depends on the amount ingested is also unclear, although some studies have suggested that symptoms appear earlier in patients who have consumed larger amounts of the solvent.²

The lethal dose of methanol varies but is generally about 30 ml.⁶ Bennett and colleagues² described one patient who had consumed 15 ml of 40% methanol and died, and another who had consumed 500 ml of absolute methanol and survived. It is interesting to speculate as to what determines this variability. The concomitant consumption of ethanol may well offer some protective effect. Also, the occurrence of chronic liver disease may alter the metabolism of methanol through its effect on the hepatic concentration of alcohol dehydrogenase. Of the five patients in our series with chronic alcoholism two had consumed ethanol with the methanol. Four of the five survived despite high levels of methanol initially, but the outcome might have been influenced by the relatively short interval between ingestion and the start of therapy.

The toxicity of methanol is related to the marked

metabolic acidosis that follows ingestion. The acidosis is largely attributed to the formic acid produced when methanol is metabolized;⁷ however, other organic acids, such as lactic acid, may also contribute.⁸ Whatever the exact mechanism, the mortality in our patients was best related to the severity of the acidosis. Only one patient with a serum bicarbonate level of less than 10 mmol/l survived, and the mean pH and serum bicarbonate levels differed significantly between the patients who survived and those who died. In Bennett and colleagues' series of 323 patients the mortality was 19% when the carbon dioxide combining power was less than 20 mmol/l and 50% when it was less than 10 mmol/l.² Moreover, the occurrence of visual complications may correlate with the degree of acidosis.⁹

The interval between ingestion and the start of therapy appears to be a very important determinant of survival. In our series the earlier treatment was started the better were the chances of survival. Moreover, early intervention decreases the rate of methanol metabolism, thus reducing the degree of metabolic acidosis. The lack of correlation between the initial blood methanol levels and the outcome can be explained by the fact that the most important determinant of outcome is the amount of methanol that has been metabolized before therapy is started. Patients for whom the interval between ingestion and presentation is long may well have a low serum methanol level, most of the methanol having been metabolized before presentation, as in our patient 4. Conversely, a patient who presents early after ingestion with a high serum methanol level may survive following prompt therapy, as our patient 7 did.

The autopsy findings in patients who have died of methanol poisoning include cerebral edema, fatty infiltration of the liver and, occasionally, acute hemorrhagic pancreatitis.² Demyelination of the optic nerves is also common.⁴ Orthner¹⁰ reported that one third of 124 patients with methanol poisoning had evidence of symmetric necrosis of the putamen, a frequent finding in fatal cases. A postmortem examination of our patient 2 revealed marked cerebral edema, demyelination of the optic nerves and bilateral necrosis of the putamen. The anterior lobe of the pituitary was also infarcted, although it was not clear whether this was related specifically to the methanol poisoning or to the hypotension and severe metabolic derangements prior to death.

Management

Successful management of methanol poisoning requires prompt recognition, for the most important therapeutic consideration appears to be early and aggressive correction of any metabolic acidosis. Therefore, diagnosis must be rapid in patients with metabolic acidosis in whom poisoning is suspected. Ethanol therapy might even be considered while the serum is being screened for drugs and assayed for methanol.

Treatment of methanol poisoning with ethanol is based on the fact that both methanol and ethanol are metabolized by alcohol dehydrogenase, but the affinity of this enzyme is greater for ethanol than for methanol. When the serum ethanol concentration is 100 mg/dl the alcohol dehydrogenase in the liver is almost completely saturated with ethanol,¹¹ so that methanol metabolism is

Table II—Serum levels of methanol and ethanol according to duration of dialysis

Duration of dialysis (h)	Serum level (mg/l)*			
	Patient 4		Patient 11	
	Methanol	Ethanol	Methanol	Ethanol
0	640	—	2649	1500
2	292	786	1835	2750
4	120	947	716	4600
6	131	1609	358	1270
8	96	2470	—	—

*Precision of measurement $\pm 10\%$ for methanol and $\pm 8\%$ for ethanol.

retarded and the methanol is excreted through the lungs and kidneys. In addition, more methanol is available for clearance by dialysis.

The pharmacokinetics of ethanol metabolism are complicated¹² and vary between patients.¹³ The desired therapeutic level in the serum of 100 mg/dl can be achieved in a variety of ways, and the results of therapy can be monitored with serial determinations of the level. Oral administration is preferred; we recommend 0.6 to 1.0 g/kg body weight either as absolute ethanol or as a 50% solution either by mouth or via a nasogastric tube.¹ We used this method in eight of our patients, and in all of them the resultant serum ethanol level was about 100 mg/dl. A therapeutic level can be maintained with subsequent doses of 10 to 15 g of ethanol per hour. To avoid a reduction in the level during hemodialysis the maintenance dose can be increased or, preferably, ethanol can be added to the dialysate for a concentration of 100 mg/dl. The latter method gave satisfactory results in all the patients in our series who underwent hemodialysis. The serum ethanol level should be monitored frequently because it is highly variable, as Table II shows.

What is the role of dialysis in the treatment of methanol poisoning? Although peritoneal dialysis has been attempted in several cases,¹⁴ including one in our series, it is less efficient and should probably be used only when hemodialysis is not available.

Hemodialysis for the treatment of methanol poisoning was first reported in 1961¹⁵ and was reviewed in 1978 by Gonda and associates.⁸ This method appears ideal because methanol, owing to its low molecular weight, is easily dialysed, as are its toxic metabolic products.¹⁶ Furthermore, hemodialysis facilitates the correction of metabolic acidosis and other accompanying metabolic derangements and helps maintain a therapeutic ethanol level.

We used a single-pass delivery system and a dialyser coil with a large surface area to keep the blood flow as high as possible. We found that the dialysance of methanol was 100 to 200 ml/min and was dependent on the rate of blood flow, which is in agreement with previous reports.^{5,9} Temporary femoral or subclavian venous catheters are the preferred routes of vascular access, as they are easily placed at the bedside and usually allow adequate rates of blood flow. The placement of an arteriovenous shunt takes time and, as therapy should be started early, may be less desirable.

Recommendations concerning the additional details of hemodialysis are unclear. Although an acetate bath was used in six of nine patients in our series, it could be argued that a bicarbonate bath would have been more appropriate, as all these patients had severe acidosis and required bicarbonate replacement. The metabolism of acetate during dialysis has not been studied in patients with severe acidosis, and, theoretically, excessive levels of acetate might aggravate the acidosis. That there were no substantial problems with hemodialysis in this and other reported series suggests that the minor details of this technique are not likely to be as important as early intervention.

The indications for hemodialysis in treating methanol poisoning are unclear, some authors suggesting its use

when the serum methanol level is greater than 100 mg/dl¹⁷ and others when the level exceeds 50 mg/dl.⁸ However, from our experience we believe that the initial methanol level should not be the sole consideration; one must allow for the degree of acidosis and the interval between ingestion and presentation for treatment. Furthermore, if a large amount of methanol has been consumed or visual disturbances are evident, methanol metabolism should be reduced immediately. Partial or total visual acuity can be restored after appropriate treatment,² as in one of our patients.

We recommend that hemodialysis be instituted promptly, independent of the initial serum methanol level, if one of the following features is present: (a) metabolic acidosis, (b) visual disturbance or (c) a history of ingestion of more than the accepted minimum fatal dose (30 ml of absolute methanol). In conjunction with alkali and ethanol therapy, hemodialysis should probably be continued until methanol can no longer be detected in the blood, thereby ensuring removal of toxic metabolites and correction of metabolic acidosis. It is unlikely that many patients will present with a detectable methanol level and not have one of the suggested indications for hemodialysis; therefore, hemodialysis should be considered when any methanol can be detected in the blood.

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